Wallace H. Clark, Jr., M.D.: A Biography and Annotated Bibliography

Wallace Clark, Jr. was born and raised in La Grange, Georgia, the son of a much loved and respected country doctor. He was schooled at The Citadel in Charleston, and at Tulane University in New Orleans. In 1944 he entered Tulane University School of Medicine, from which he graduated with an M.D. in 1947. He trained in Pathology at Tulane University and in the Touro Infirmary of New Orleans. After two years in the Service, he became Assistant Professor and later Associate Professor and Professor (at the age of 36) in the Tulane Department. At Tulane, Clark developed seminal concepts of pattern pathology applied especially to dermatopathology that were ultimately to revolutionize the field. He also became expert in the use of a novel high-tech instrument, the electron microscope, applying it to the examination of skin and providing original descriptions of the mela-nocyte, the melanosome, and several basic attributes of keratinocyte morphology. At Tulane Clark's thinking about research and life was profoundly altered by association and friendship with Emmanuel Farber, now at the University of Toronto. He also developed a collaboration and deep friendship with Richard Reed in the study of cutaneous disease. These Tulane associations have persisted throughout Clark's life. In the same period, Clark was a consultant to the Orleans Parish Coroner's Office. There are rumors that a certain celebrated television pathologist was loosely based on the flamboyant New Orleans coroner's pathologist of the late 1950 and early 1960 decades. In 1962, Clark was recruited by Thomas Fitz-patrick and Benjamin Castleman to the Massachusetts General Hospital. In the stimulating environment of the Departments of Pathology and of Dermatology at the Harvard Medical School, Clark continued to develop his concepts of the reaction patterns and morphologic units of inflammatory disease in the skin. These concepts were taught to several generations of residents, many of whom later became influential in the fields of surgical pathology and dermatopathology. At Harvard also, Clark developed his lifelong passion for the morphology and biology of the neoplastic diseases of pigment cells. With Fitzpatrick, he founded the first Pigmented Lesion Clinic, a model for hundreds of its ilk that now exist worldwide. In 1974, Clark became Chairman of Pathology at Temple University School of Medicine in Philadelphia. There he continued his basic research in melanocytic carcinogenesis, developed a fine cutaneous electron microscopy unit, established the first Pigmented Lesion Clinic in Philadelphia, and administered a complex department while training residents not only in diagnostic anatomic pathology but also in his scientific approach to the study of disease. Several individuals recruited in the Temple Clinic including Jean Thompson, Marie Synnestvedt, Bill Witmer, and Isabel Mattozzo were to remain with Clark until his retirement in 1991, as were many of the patients who were seen there. In 1978, Clark moved across town to the Dermatology Department at the University of Pennsylvania, chaired by Walter Shelley, in a recruitment effected in part by Albert Kligman. An already extant collaboration with Hilary Koprowski at the Wistar Institute across the street burgeoned into a program project to comprehensively study aspects of melanoma cell biology, using the state of the art technology of the late 1970s, monoclonal antibodies. Now under the leadership of Meenhard Herlyn, this collaboration continues into the present molecular era. At Penn, Clark recruited other collaborators who were to continue as lifelong friends and colleagues, including Dupont Guerry, Ralph Hamilton, Donato LaRossa, and Edward Bondi and David Elder (who had moved with him from Temple). To these founding members of the Pigmented Lesion Group at Penn, Allan Halpern, Lynn Schuchter, George Murphy, and Rosalie Elenitsas have been added. In ''retirement'' since 1991, Clark lives in Maine but commutes weekly into the Department of Pathology at the Beth Israel Hospital where he consults, teaches, reads, and talks about cancer. He also retains an Emeritus Professorship at the University of Pennsylvania where he continues to contribute to the Pigmented Lesion Group and the Dermatopathology Division.

Recently it has become fashionable to acknowledge the term ''physician-scientist'' as an oxymoron. To the contrary, Wallace Clark's approach to the practice of pathology has never distinguished between the applied and the theoretical. In fact each serves to fuel the other. Assigning diagnoses is never employed merely to ''give something a name so as to stop thinking about it.'' Rather, diagnostic recognition always stimulates a flood of questions concerning the biologic basis of a lesion's cause, evolution, and resolution. Accordingly, what could have seemed routine becomes the fundamental basis for scientific exploration, whereas more basic investigations always are tightly linked to clinically relevant aspects of patient care. As opposed to the present trend to discourage this approach as impractical or even impossible, young physician-scientists continue to be spawned from this paradigm he embodies.

Although Wallace Clark is well recognized as a physician, scientist, and teacher, those privileged to know him on a personal level consider him, above all, an intellectual. An intellectual not only concerns himself with ideas and concepts, but, as Isaiah Berlin said, ''wants ideas to be as interesting as possible.'' This is the strategy that Wallace applies not only to dermatopathology, but to all his endeavors. He does not just describe or document in a static manner; rather he tries to enter, view from the ''inside,'' and in this manner being inert situations to life. Outside the laboratory, conversations with Wallace reflect his wide scope of non-scientific, intellectual passions. These discussions, which can range from how homo sapien could participate in holocausts and pogroms to the *raison d'etre* behind the local team's losing streak (he never questions winning), are always thought provoking and stimulating. He is as comfortable arguing the decline of Utopian

0022-202X/93/$06.00

philosophy in the West as he is articulating a concept on the failure of higher education to educate. Being a serious student of the human condition and the diversity of cultures, Wallace constantly strives to understand what motivates people and their societies. Consequently, he is extremely well versed and learned in the philosophies underlying the major religions, as well as in theories of anthropology. Wallace's pursuits are not solely cerebral. He is an accomplished photographer (nature and people), tropical fish fancier, naturalist, bicyclist, California wine connoisseur, and raconteur as well as a devoted family man.

Wallace Clark's creativity is measured not only in the manuscripts listed below in this annotated curriculum vitae, but also in the institutions that have benefited from his organizational and motivational skills in the form of productive continuing research and clinical enterprises. Clark's formal honors are many: the Markle Scholarship while at Tulane Medical School; a Gold Award of the American Academy of Dermatology for electron microscopy of the ''intercellular bridge'' and the melanocyte in 1958; and scientific awards and lectureships too many to enumerate from institutions like the American Cancer Society, the James Ewing Society of Surgical Oncology, the Academy of Medicine of Toronto, the College of Physicians of Philadelphia, and the British Association for Cancer Research, as well as numerous University Departments and State Societies. Perhaps one of the most treasured awards was the Wallace H. Clark, Sr. lectureship in 1980. In 1991, Wallace H. Clark, Jr. was made Doctor Honors Causa of the ancient University of Liege. The most long-lived expressions of his contributions, however, will be preserved in the minds of the many individuals he has influenced, who will in turn pass along those influences in the continuing transmission of ideas that characterizes relationships among mentors, students, collaborators and, indeed, competitors in the genealogy of science.

SELECTED BIBLIOGRAPHY

Classification of Melanoma Because of Clark's expertise and commitment as both a clinician and a pathologist, he was one of the first to study malignant melanoma using both clinical and microscopic morphology as a basis to classify the lesions into stages of development that would ultimately constitute one of the best-characterized models of tumor progression in humans. The early studies resulted in three powerful concepts. First, the progression of melanomas from a plaque stage called the radial growth phase to a nodule or tumor stage called the vertical growth phase was clearly described. Second, it was recognized that variant patterns of radial growth phase could be discerned, which would later lead to the recognition of differences in etiology and pathogenesis. Third, the system of ''Clark's levels) of invasion was described, constituting the first widely used prognostic model for melanoma. Clark established a Pigmented Lesion Clinic that has served as a prototype for others that have been established world-wide to provide for multi-disciplinary care of melanoma patients, and to foster study of this important human cancer.

Clark WH Jr, Mihm MC: Lentigo maligna and lentigo-maligna melanoma. Am J Pathol 5(l):38–67, 1969

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Mihm MC Jr, Clark WH Jr, From L: Current Concepts: the clinical diagnosis, classification and histogenetic concepts of the early stages of cutaneous malignant melanoma. N Engl J Med 284:1078–1082, 1971

McGovern VJ, Mihm MC Jr, Bailly C, Booth JC, Clark WH Jr, Cochran AJ, Hardy EG, Hicks JD, Levene A, Lewis MG, Little JH, Milton GW: The classification of malignant melanoma and its histologic reporting. Cancer 32(6):1446–1457, 1973

Clark WH Jr, Ainsworth AM, Bernardino EA, Yang CH, Mihm MC Jr, Reed RJ: The developmental biology of primary human malignant melanomas. Semin Oncol 2(2):83–103, 1975

Clark WH Jr, Folberg R, Ainsworth AM: Tumor progression in primary human cutaneous malignant melanoma. In: Clark WH Jr, Goldman LI, Mastrangelo MJ (ed). Human Malignant Melanoma. Grune and Stratton, New York, 1979, pp 15–31

Clark WH Jr, Elder DE, Van Horn M: The biological forms of malignant melanoma. Hum Pathol 17(5):443–450, 1986

Several papers dealt explicitly with the early diagnosis of melanoma. Clark's early observations have by now become accepted as common wisdom, and have undoubtedly saved countless lives that might have been lost to advanced melanomas had not this knowledge become available.

Sober AH, Fitzpatrick TB, Mihm MC, Wise TG, Pearson BJ, Clark WH Jr, Kopf AW: Early recognition of cutaneous melanoma. JAMA 242:2795–2799, 1979

Wick MM, Sober AJ, Fitzpatrick TB, Mihm MC, Kopf AW, Clark WH, Blois MS: Clinical characteristics of early cutaneous melanoma. Cancer 45(10):2684–2686, 1980

Animal models were used to establish models of tumor progression analogous to that observed in humans.

Clark WH Jr, Min BH, Kligman LHL: The developmental biology of induced malignant melanoma in guinea pigs and a comparison with other neoplastic systems. Cancer Res 36:4079–4091, 1976

Oxenhandler RW, Adelstein RH, Haigh JP, Hook RR Jr, Clark WH Jr: Malignant melanoma in the Sinclair miniature swine: an autopsy study of 60 cases. Am J Pathol 96(3):707–720, 1979

Prognostic Models in Melanoma In his early studies of melanoma, Clark recognized that the lesions could be categorized in terms of their invasion ''level'' into the skin, and that this classification correlated with prognosis. The system of ''Clark levels'' became universally adopted as the basis of rational therapy for melanoma, and stimulated investigations that revealed other factors contributing to survival, such as tumor thickness. At the same time, a concept was developed of tumor progression from an early ''radial growth phase'' that was not associated with metastatic competence despite the presence of dermal invasion. Many of these studies, including the latest prognostic model in which six variables are associated with survival, were developed using the Pigmented lesion Group database, established and maintained by Clark, that presently includes clinical, pathologic, and follow-up data on over 3000 melanoma cases.

Clark WH Jr: A classification of malignant melanoma in man correlated with histogenesis and biological behavior. In: Advances in Biology of Skin. Vol VIII: The Pigmentary System. Pergamon Press, New York, 1967, pp 621-647.

In a study from the first five years of the Pigmented Lesion Group experience at Penn, the hypothesis that invasive radial growth phase melanoma does not metastasize was tested.

Elder DE, Guerry D IV, Epstein MN, Zehngebot L, Lusk E, Van Horn M, Clark WH Jr: Invasive malignant melanomas lacking competence for metastasis. Am J Dermatopathol 6(suppl 1):55–61, 1984

The predictive value of invasion levels was tested in several clinical studies (and was also confirmed in studies by other investigators).

Goldman LI, Clark WH Jr, Bernardino EA, Ainsworth AM: The accuracy of predicting lymph node metastases in malignant melanoma by clinical examination and microstaging. Ann Surg 184(5):537–540, 1976

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Holmes EC, Clark WH Jr, Morton DL, Eilber FR, Bochow AJ: Regional lymph node metastases and the level of invasion of primary melanomas. Cancer 37:199–201, 1976

In a recent study of cases from the Pigmented Lesion Group database with eight-year follow-up, the hypothesis that tumor progression from radial to vertical growth phase is associated with acquisition of competence for metastasis was confirmed. Six independent variables associated with survival in vertical growth phase cases were identified, including lesional thickness, mitotic rate, tumor-infiltrating lymphocytes, presence of regression, sex of the patient, and location of the lesion on anatomic subsites.

Clark WH, Elder DE, Guerry DG, Braitman LE, Track BJ, Schultz MA, Synnestvedt M, Halpern AC: A model predicting survival in stage I melanoma based upon tumor progression. J Natl Cancer Inst 81:1893–1904, 1989

Diagnosis and Management of Melanoma Arising out of the clinical activities in the three pigmented lesion clinics established by Clark at Harvard, Temple, and Penn, a series of clinical studies has played a significant role in defining management of melanoma. The clinical recognition of melanomas in the early curable radial growth phase was a major theme, as was the potential role of education in control of mortality from melanoma by means of early diagnosis

Holmes EC, Moseley HS, Morton DL, Clark WH Jr, Robinson D, Urist MM: A rational approach to the surgical management of melanoma. Ann Surg 186(4):481–490, 1977

Cassileth BR, Clark WH Jr, Heiberger RM, March V, Tenaglia A: Relationship between patients' early recognition of melanoma and depth of invasion. Cancer 49:198–200, 1982

Elder DE, Guerry DIV, Heiberger RM, LaRossa D, Goldman LI, Clark WH Jr, Thompson CJ, Matozzo I, Van Horn M: Optimal resection margin for cutaneous malignant melanoma. Plast Reconstr Surg 71(l):66–72, 1983

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Clark WH Jr, Elder DE, DuPont G IV: The pathogenesis and pathology of dysplastic nevi and malignant melanoma. In: Farmer E, Hood A (ed). The Pathology of the Skin. Appleton-Century-Crofts, New York, 1990

A book was published describing concepts of melanoma biology and early notions about the significance of nevi in melanoma risk and pathogenesis.

Clark WH Jr, Goldman LI, Mastrangelo MJ: Human Malignant Melanoma. Grune and Stratton, New York, 1979, pp 1–509

Three educational videotapes were produced for families, clinicians, and pathologists dealing with the subject of dysplastic nevi in hereditary melanoma kindreds. These were widely disseminated by the National Cancer Institute.

Elder DE, Clark WH Jr, Control and prevention of melanoma: a program for melanoma-prone families. Videotape educational program produced for Environmental Epidemiology Branch, National Cancer Institute (30 min), 1980

Elder DE, Clark WH Jr: Dysplastic nevi and melanoma: a program for pathologists. Videotape educational program produced for Environmental Epidemiology Branch, National Cancer Institute (30 min), 1980

Elder DE, Clark WH Jr, Greene MH: Dysplastic nevi and melanoma: a program for clinicians. Videotape produced for Environmental Epidemiology Branch, National Cancer Institute (57 min), 1980

Dysplastic and Congenital Melanocytic Nevi Although melanocytic nevi are ubiquitous benign neoplasms of the skin, their significance in tumor progression and in the pathogenesis of melanoma was not recognized until recently, with Clark's investigations and teaching playing the major role in this recognition. The first of these studies was influential in the developing understanding of congenital nevi and their potential role in melanoma pathogenesis.

Mark GJ, Mihm MC Jr, Liteplo MG, Reed RJ, Clark WH Jr: Congenital melanocytic nevi of the small and garment type: clinical, histological, and ultrastructural studies. Hum Pathol 4(3):295–418, 1973

With Mark Greene of the NCI, Clark first recognized the significance of large, clinically atypical nevi as markers of melanoma risk in members of hereditary melanoma-prone kindreds, and in a series of classic papers the clinical and histologic attributes of these lesions were defined.

Greene MH, Reimer RR, Clark WH Jr, Mastrangelo MJ: Precursor lesions in familial melanoma. Semin Oncol 5(l):85–87, 1978

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In later studies, the epidemiologic significance of dysplastic nevi in melanoma-prone kindreds was elucidated.

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In the Pigmented Lesion Clinic, it was first recognized that dysplastic nevi were commonly associated with sporadic as well as hereditary melanoma.

Elder DE, Goldman LI, Goldman SC, Greene MJ, Clark WH Jr: Dysplastic nevus syndrome: a phenotypic association of sporadic cutaneous melanoma. Cancer 46(8):1787–1794, 1980

The role of dysplastic nevi as potential precursors of hereditary melanoma was clearly recognized in the early papers and their important role in sporadic melanoma was further defined in studies from the Pigmented Lesion Group database.

Clark WH Jr, Elder DE, Guerry D IV, Epstein MN, Greene MH, Van Horn M: A study of tumor progression: The precursor lesions of superficial spreading and nodular melanoma. Hum Pathol 5(12):1147–1165, 1984

Collaborative studies with Greene and others ultimately led to mapping of a melanoma susceptibility gene onto the short arm of chromosome 1.

Greene MH, Goldin LR, Clark WH Jr, Lovrien E, Kraemer KH, Tucker MA, Elder DE, Fraser MC, Rowe S: Familial cutaneous malignant melanoma: autosomal dominant trait possibly linked to the *Rh* locus. Proc Natl Acad Sci 80:6071–6075, 1980

Bale SJ, Dracopoli NC, Tucker MA, Clark WH Jr, Frazer MC, Stanger BZ, Green P, Donis-Keller H, Housman DE, Greene MH: Mapping the gene for hereditary cutaneous malignant melanoma-dysplastic nevus to chromosome 1 p. NEngl J Med 310:1367–1372, 1988

Screening and surveillance of members of hereditary melanoma kindreds in the Pigmented Lesion Clinic has led to diagnosis of melanomas at an earlier, more curable stage of their evolution.

Masri GD, Clark WH, Guerry DG, Halpern A, Thompson CJ, Elder DE: Screening and surveillance of patients at high risk for malignant melanoma results in detection of earlier disease. J Am Acad Dermatol 22:1042–1048,1990

Biology of Melanoma In 1978, Clark with Koprowski and later Herlyn of the Wistar Institute established and has since maintained a productive long-term collaboration of basic and clinical scientists. This collaboration resulted in the first production of monoclonal antibodies to melanoma antigens, and to a body of cell culture and cytogenetic work. Clark's central hypothesis of tumor progression from radial to vertical growth phase in melanoma has provided an essential focus for these studies. This interdisciplinary research would not have been possible without the establishment of this complex cooperative group of investigators at two institutions.

Melanoma-Associated Antigens Monoclonal antibodies have been used to explore the antigenic phenotype of melanomas and to search for therapeutically active agents.

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Thompson JJ, Herlyn MF, Elder DE, Clark WH Jr, Steplewski Z, Koprowski H: Expressions of DR antigens in human tumors. Hybridoma 1(2):161–168, 1982

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Iliopoulos D, Ernst C, Steplewski Z, Jambrosic JA, Rodeck U, Herlyn M, Clark WH Jr, Koprowski H, Herlyn D, Iliopoulos DC: Inhibition of metastases of a human melanoma xenograft by monoclonal antibody to the G_{D2}/G_{D3} gangliosides. J Natl Cancer Inst 81:440–444, 1989

Monoclonal antibodies have also been used to examine mechanisms of tumor progression in melanoma.

Thurin J, Thurin M, Herlyn M, Elder DE, Steplewski Z, Clark WH Jr, Koprowski H: G_{D2} ganglioside biosynthesis is a distinct biochemical event in human melanoma tumor progression. Fed Eur Biochem Soc 208(1):17–22, 1986

Elder DE, Ulrich R, Thurin J, Cardillo F, Clark WH, Stewart R: Antigenic profile of tumor progression stages in human melanocytic nevi and melanomas. Cancer Res 49(18):5091–5096, 1989

Cytogenetics and Cell Biology Cytogenetic studies have explored mechanisms of tumor progression in melanoma.

Balaban G, Herlyn M, Guerry D IV, Bartolo R, Koprowski H, Clark WH, Nowell PC: Cytogenetics of human malignant melanoma and premalignant lesions. Cancer Genet Cytogenet 11:429–439, 1984

Balaban GB, Herlyn M, Clark WH Jr, Nowell PC: Karyotypic evolution in human malignant melanoma. Cancer Genet Cytogenet 19:113–122, 1986

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Parmiter AH, Balaban G, Herlyn M, Clark WH Jr, Nowell PC: A t (1;19) translocation in three cases of human malignant melanoma. Cancer Res 46:1526–1529,1986

Studies of growth characteristics of melanoma cells in culture have confirmed that cells of the vertical growth phase have biologic capacities similar to those of cells from metastases.

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Electron Microscopy of the Skin In 1958, Clark pioneered the use of the newly developed tool of electron microscopy to begin a series of studies of the skin and its constituent cells, publishing the first description of the melanosome, the organelle that specifically identifies the melanocyte, and in which melanin pigment is synthesized.

Clark WH Jr, Hibbs RG (with the technical assistance of Watson M): Electron microscope studies of the human epidermis: the clear cell of Masson (dendritic cell or melanocyte). J Biophys Biochem Cytol 4(6):679–684, 1958

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Leone P, Clark WH Jr: Ultrastructure of the intra-epidermal melanocyte of the melanocytic nevus. Lab Invest 24:438, 1971

Clark WH Jr: Four types of cellular fine structure associated with human amelanotic melanoma. Yale J Biol Med 46:428, 1972

Roth SI, Clark WH Jr: Ultrastructural evidence related to the mechanism of keratin synthesis. In: Montagna W, Lobitz WC Jr (ed.). The Epidermis. Academic Press, New York, 1964, pp 300–337

Clark WH, Bretton R: A comparative fine structural study of melanogenesis in normal human epidermal melanocytes and in certain human malignant melanoma cells. In: Helwig EB (ed.). The Skin, International Academy of Pathology. The Williams & Wilkins Co., Baltimore, MD, 1971, pp 197–214

Clark WH Jr, Heggeler BT, Bretton R: Electron microscope observations of human cutaneous melanomas correlated with their biologic behavior. Presented at The International Cancer Conference, 1972, Sydney, Australia. In: Melanoma and Skin Cancer. Sydney, Australia: VCN Blight, Government Printer, pp 121–141

Contributions to Diagnostic Dermatopathology Although a few scholars in Europe and the older US medical schools were developing the field, dermatopathology was still in a primitive state in the middle of this century. Working in New Orleans and trained as a general pathologist, Clark began a series of papers that would ultimately constitute a body of original work that has made major contributions to diagnostic dermatopathology, extending well beyond his primary interest in the melanocytic tumors. In addition to his published work, Clark's ideas have been further developed and disseminated by his many talented students.

Ackerman AB, Penneys NS, Clark WH: Erythema multiforme exudativum: distinctive pathological process. Br J Dermatol 84:554–565, 1971

Clark WH, Reed RJ, Mihm MC: Lupus Erythematosus: histpathology of cutaneous lesions. Hum Pathol 4(2):157–163, 1973

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Nigra TP, Soter NA, Clark WH Jr, Tolman MM: Vesicular and bullous diseases: dermatitis herpetiformis. In: Fitzpatrick TB (ed.). Dermatology in General Medicine. McGraw-Hill, Inc., New York, 1971, pp 618–621

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